ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 11, Issue, 08, pp. 49807-49809, August, 2021
https://doi.org/10.37118/ijdr.22762.08.2021

RESEARCH ARTICLE OPEN ACCESS

PECULARITIES OF BONE DISEASE IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

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ARTICLE INFO

Article History:
Received 20th May, 2021
Received in revised form
23rd June, 2021
Accepted 19th July, 2021
Published online 29th August, 2021

Key Words:

Elderly, Chronickidneydisease in Elderly, Kidneyandaging, Ecularities of kidneydisease in elderly.

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ABSTRACT

Background: Chronic kidney disease has a high prevalence in Brazil and worldwide, being a growing public health problem that generates disabilities, early mortality and costs for health systems, causing great harm to the patient's bone health and harming metabolic and hemodynamic control and compromised quality of life. The various functions of the kidneys are influenced by the complex process of normal aging, and the progress of this process can be influenced by overlapping diseases. Microscopically, the numbers of nephrons decrease as global glomerulosclerosis becomes more evident. The precise mechanisms underlying nephron loss with aging are not well understood, but disturbances in podocyte biology appear to be. CKD classification incorporates GFR values and risk resulting from adverse events. In this way, arbitrary and fixed GFR thresholds for the definition of CKD have led to an overdiagnosis of CKD in the elderly. **Objective:** To discuss if an age-sensitive definition of CKD could offer a solution to this problem and capture more significantly the prognostic implications of CKD and, in particular, may be different in "healthy" aging compared to disease-induced pathology. **Methods:** review data on the topic in the literature and consider different points of view. **Results:** Although without robust studies,some of them points to exaggerated diagnoses of chronic kidney disease in the elderly and agree on the need to reassess the classification of the disease in the elderly population.**Conclusions:**With population aging and the increase in chronic diseases, it is essential to distinguish between physiological aging processes and diseases themselves, in order to favor more appropriate approaches and conduct.

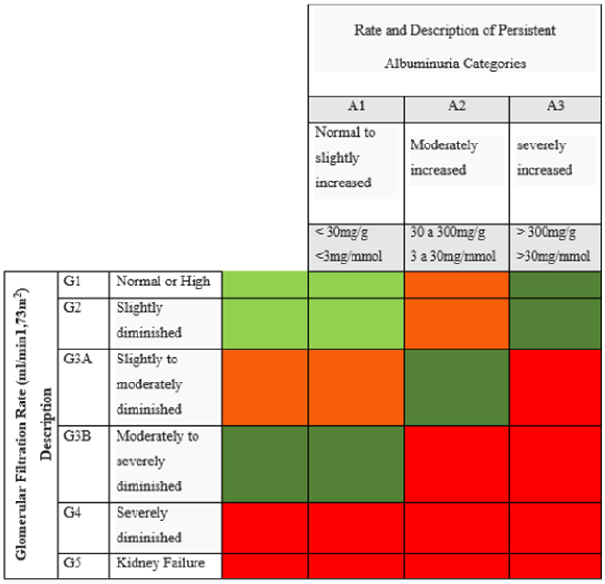
Citation: ***Fernanda Silveira Tavares, Lucy de Oliveira Gomes, Ana Rachel Teixeira Batista Carvalho, DilsonPalhares Ferreira et al.*** "Pecularities of bone disease in elderly patients with Chronic Kidney Disease*", International Journal of Development Research*, 11, (08), 49807-49809.

INTRODUCTION

The kidneys play a crucial role in the control of blood pressure and volume, hydroelectrolyte and acid-base balance, erythropoietin secretion, site of activity of the renin-angiotensin-aldosterone system (SARS) and, recently, have gained importance with studies about of sodium and glucose cotransporter receptors type 2 (SGLT-2) (Benzing 2021)by coronavirus tropism for renal tubules (Martinez-Rojas, Vega-Vega, and Bobadilla 2020), added to molecular biology and genetic studies (Palau *et al*. 2019), thus making the renal physiology and pathophysiology of diseases that affect the kidneys more understandable (Su *et al*. 2020). When kidney damage is present, the repercussions are reflected throughout the body, with high rates of morbidity and mortality in patients with significant dysfunction (Sarnak *et al*. 2019)(Kadkhodaee *et al*. 2012).Adequate renal function is therefore vital for the entire body (Risso *et al*. 2019). The nephron is the functional unit of the kidneys, being responsible for filtration, reabsorption, secretion and excretion (Nieskens and Sjögren 2019). All renal functions usually decline in parallel with their excretory function, called the Glomerular Filtration Rate (GFR) (Solomon and Goldstein 2017). The measurement of GFR is an essential tool to determine kidney health or dysfunction (T. Wang *et al*. 2019), and can be measured through different types of calculations (Neuma De Souza Brito *et al*. 2016), Cockcroft-Gault (CG), Diet Modification in Kidney Disease (MDRD) and CKD-EPI (Collaboration in Chronic Kidney Disease Epidemiology) formulas are often used to estimate GFR (Drenth-van Maanen *et al*. 2013). All of these formulas are age-influenced and can be used for older people, but overall the CKD-EPI provides the best estimate of GFR, although its accuracy is close to that of DMKD (Drenth-van Maanen *et al*. 2013).

Chronic kidney disease has a high prevalence in Brazil and worldwide, being a growing public health problem that generates disabilities, early mortality and costs for health systems, causing great harm to the patient's bone health and harming metabolic and hemodynamic control and compromised quality of life (Graciolli *et al*. 2017). The various functions of the kidneys are influenced by the complex process of normal aging, and the progress of this process can be influenced by overlapping diseases (Hommos, Glassock, and Rule 2017). Microscopically, the numbers of nephrons decrease as global glomerulosclerosis becomes more evident (Bellorin-Font, Vasquez-Rios, and Martin 2019). The precise mechanisms underlying nephron loss with aging are not well understood, but disturbances in podocyte biology appear to be involved (Denic, Glassock, and Rule 2016). CKD classification incorporates GFR values and risk resulting from adverse events (Glassock and Rule 2016). Arbitrary and fixed GFR thresholds for the definition of CKD have led to an overdiagnosis of CKD in the elderly (Brown *et al*. 2017). An age-sensitive definition of CKD could offer a solution to this problem and capture more significantly the prognostic implications of CKD (Portilla Franco, Molina, and Gregorio 2016) (Morgan, Wong, and Finch 2007) (Figure 10).

All human organs and organ systems exhibit the consequences of aging, but this brief review will focus primarily on the kidneys, specifically the glomeruli and their function (Wang *et al*., 2014). Several other functions of the kidneys, such as concentration and dilution of urine and sodium and potassium homeostasis, can also be influenced by the aging process (Lindeman, Tobin, and Shock 1985). The normal GFR in a healthy adult male at age 20 is about 100–110 ml / min / 1.73 m^2 and may decrease to <60 ml / min / 1.73 m^2 at a variable fraction (5 to 25%) of healthy adults aged 60 to 65 years (Hommos, Glassock, and Rule 2017). The GFR frequency distribution remains approximately Gaussian at all ages and the decline in GFR with aging is independent of blood pressure in healthy non-hypertensive individuals (Neuma De Souza Brito *et al*. 2016). The fundamental origins of declining GFR with healthy aging is not fully understood (Wang *et al*. 2014). With aging, kidneys and cortical volume decrease (in parallel with declining GFR), while medullary volume increases in some elderly people (Wang *et al*. 2014).



CKD is classified based on cause, GFR category (G1 to G5) and albuminuria category (A1 to A3). Green means low risk (no CKD if no other markers of kidney disease), yellow means moderately increased risk, orange means high risk, and red means very high risk for functional impairment.(Reproduced with permission from Kidney Disease: Improving Overall Outcomes).

Figure 1. From: Diagnosis, Assessment, Prevention and Treatment of Chronic Kidney Disease - Mineral and Bone Disorder: Kidney Disease Synopsis: Improving Overall Outcomes Clinical Practice Guideline Update 2017 Adapted by the authors

In that aspect, renal aging is characterized by nephrosclerosis, increased focal and global concentration, non-segmental glomerulosclerosis, interstitial fibrosis, tubule atrophy and arteriolosclerosis (Kremers *et al*. 2015). The clinical importance of this glomerulosclerosis, in particular, may be different in "healthy" aging compared to disease-induced pathology (Bikbov *et al*. 2020) (Chen, Knicely, and Grams 2019) (Portilla Franco, Molina, and Gregorio 2016). It is debatable whether these GFR values measured in elderly individuals contribute to the determination of risks of adverse cardiovascular events (CVD) or mortality (Clase *et al*. 2011). Adding GFR-based CKD stage to standard risk prediction (Framingham Risk Scores) for CVD events does not improve risk ranking, and GFR has not been incorporated into most of these scoring systems widely used in clinical practice (Malmgren *et al*. 2015). In an exhaustive meta-regression analysis involving CKD, (Hallan *et al*. 2012) showed that the relative risk of all-cause mortality associated with a decline in GFR (adjusted for albuminuria and comorbidity) is attenuated by age. However, using a common reference point of a GFR of 80 ml/min/1.73 m^2 the risk of mortality increased at all ages when the GFR dropped below 60 ml/min/1.73 m^2. There has been much debate about whether a relative risk of mortality greater than 20% in Stage 3A CKD in the elderly would be important, because it would translate into a high absolute risk of mortality. This researcher concludes that an ideal CKD classification system should justify how well it detects the absolute risk of mortality in this population, and it would also need to take into account the limited human life expectancy. Furthermore, it remains debatable whether there really is an increased risk of mortality in all age groups for CKD Stage 3A (Hallan *et al*. 2012).Above this stage, pathological processes favor the decline of renal function in this population (Delanaye *et al*. 2019). Based on these considerations, a classification was proposed to modify the risk stratification for individuals above and below 65 years of age(Andrassy 2013). If this proposal were adopted, the prevalence of CKD stratified by prognosis (risk) in general adult populations could decrease from about 11 to 13 to 5% or less, and referrals for assessment of “alleged” CKD in the elderly could be reduced by 70% or more(Andrassy 2013). This would reflect a better definition and differentiation between physiological and pathological processes of aging and would establish better risk stratification of evolution, mortality and cardiovascular risk (Musso and Oreopoulos 2011).

In summary, although still without robust studies, some of them points to exaggerated diagnoses of chronic kidney disease in the elderly and agree on the need to reassess the classification of the disease in the elderly population.With population aging and the increase in chronic diseases, it is essential to distinguish between physiological aging processes and diseases themselves, in order to favor more appropriate approaches and conduct.

Conflicts of Interest: the authors declare that there are no conflicts of interest in this review.

Glossary of Abbreviations

CG Cockcroft-Gault
CKD Chronic Renal Disease
CKD-EPI Collaboration in ChronicKidneyDiseaseEpidemiology
CVD Cardiovascular Disease
DMKD DietModifiction in Kidney Disease
GFR Glomerular Filtration Rate

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